

ALKoma: A Cancer Subtype with a Shared Target

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ABSTRACT

Anaplastic lymphoma kinase (ALK) is a receptor-type protein tyrosine kinase that is currently the focus of much attention in oncology. ALK is rendered oncogenic as a result of its fusion to NPM1 in anaplastic large cell lymphoma, to TPM3 or TPM4 in inflammatory myofibroblastic tumor, to EML4 in non-small cell lung carcinoma, and to VCL in renal medullary carcinoma. It is also activated as a result of missense mutations in neuroblastoma and anaplastic thyroid cancer. Whereas these various tumors arise in different organs, they share activated ALK, and a marked clinical efficacy with ALK inhibitors has already been shown for some of the tumors with ALK fusions. One of such compound, crizotinib, is now approved in the United States for the treatment of lung cancer positive for ALK rearrangement. I propose that tumors carrying abnormal ALK as an essential growth driver be collectively termed “ALKoma.”

Significance: ALK acquires transforming ability through gene fusion or missense mutation in a wide range of human cancers. Some of these cancers, which I propose be collectively referred to as “ALKoma,” may all be effectively treated with small compounds or antibodies targeted to activated ALKs. *Cancer Discov*; 2(6); 495–502. ©2012 AACR.

INTRODUCTION

Anaplastic lymphoma kinase (ALK) is a protein tyrosine kinase (PTK) that possesses a single transmembrane domain and consists of 1,620 amino acid residues in humans (Fig. 1; refs. 1, 2). The extracellular region of ALK contains 2 MAM (meprin, A5 protein, and protein phosphatase μ) domains (3) and a putative ligand-binding domain. ALK is relatively isolated in the phylogenetic tree of the PTK superfamily, with its kinase domain sharing the highest sequence identity with that of the leukocyte receptor tyrosine kinase (LTK; 79% identity) and that of the proto-oncoprotein ROS1 (50% identity).

In the mouse, expression of ALK is prominent in the brain and peripheral nervous system of developing embryos, but it decreases rapidly after birth. In the adult human, ALK is expressed at a low level in the central nervous system but is not detected in other tissues (4). Given these expression profiles, ALK has been thought to play an important role in the development or orchestration of the nervous system.

Surprisingly, however, homozygous deletion of *Alk* in mice does not give rise to any apparent anomalies in morphology, internal organs, or fertility, suggesting that the gene is not essential for mouse development (5). A more detailed analysis of *Alk* knockout mice revealed an increase in the number of hippocampal progenitor cells in the brain and an enhanced performance in a test of novel object recognition. Another strain of such mice manifested increased ethanol consumption compared with heterozygous controls (6). These observations thus suggest that ALK may contribute to behavioral control in adult mice.

The structure of ALK, together with its expression pattern, suggests that it may function as a cell surface receptor for specific ligands that may regulate the proliferation or differentiation of neural cells. In the fruit fly, jelly belly (*jeb*) binds and activates an ortholog of ALK (7), but a mammalian ortholog of *jeb* has not been identified. The growth factors pleiotrophin and midkine have been proposed as candidate ligands for mammalian ALK (8, 9), but this notion remains controversial (10), leaving the biologic relevance of pleiotrophin and midkine unclear.

ALK first emerged in the field of oncology in 1994 as a result of the identification of its fusion to nucleophosmin (NPM1) in anaplastic large cell lymphoma (ALCL; Figs. 1 and 2; refs. 11, 12). The NPM1 portion mediates constitutive dimerization and consequent activation of the NPM1-ALK fusion protein (13). In addition to NPM1-ALK, various other ALK fusion proteins have now been identified in ALCL, including TFG-ALK, ATIC-ALK, and CLTC-ALK. The next disease linked to ALK was inflammatory myofibroblastic

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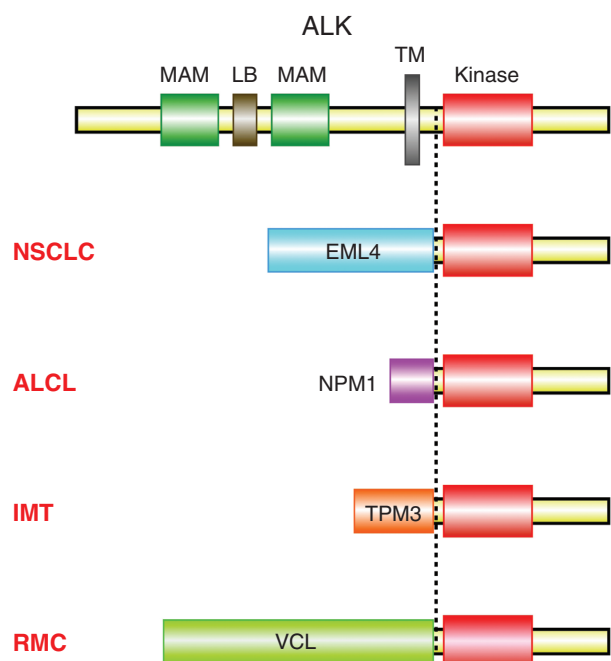


Figure 1. Structural organization of ALK and its fusion proteins. ALK is a receptor-type PTK with a single transmembrane (TM) domain as well as 2 MAM domains and a putative ligand-binding (LB) domain in the extracellular region. The intracellular region contains a kinase domain and is fused to EML4 in NSCLCs, to NPM1 in ALCLs, to TPM3 in IMTs, and to VCL in RMCs.

tumor (IMT), with increased expression of ALK and a rearranged *ALK* locus (chromosome band 2p23) being detected in a subset of IMT cases. A more detailed analysis identified *TPM3-ALK* and *TPM4-ALK* as fusion genes in IMT (Figs. 1 and 2; ref. 14). Further screening of IMT specimens revealed additional *ALK* fusions including *RANBP2-ALK* and *CARS-ALK*. Interestingly, some of these fusion genes, such as *TPM3/4-ALK* and *CLTC-ALK*, have been identified in both ALCLs and IMTs. The presence of *TPM3/4-ALK* was also reported in esophageal squamous cell carcinoma (15) and renal cancer (16).

In 2007, interest in ALK and the therapeutic potential of its specific inhibitors was boosted in response to the discovery of another fusion gene, *EML4-ALK*, this time in non-small cell lung carcinoma (NSCLC; ref. 17). Such interest was further increased the next year by the identification of activating point mutations in *ALK* in cases of neuroblastoma (18–21). In this review, I focus on activating genetic changes of *ALK* relevant to human cancer. Other aspects of *ALK* alterations (such as over-expression) in cancer have been elegantly reviewed elsewhere (22, 23).

EML4-ALK EML4-ALK in NSCLC

Chronic myeloid leukemia (CML) is characterized by the presence of a fusion-type PTK, BCR-ABL1, that is generated as a result of a balanced chromosomal translocation, t(9;22). The remarkable therapeutic efficacy of the ABL1 inhibitor imatinib in individuals with this condition (24) suggested that targeting of the essential growth drivers in different types of cancer is a promising treatment strategy. To identify such growth drivers in clinical specimens, we developed a sensitive functional screening system based on retroviral cDNA expression libraries. The application of this approach to a lung adenocarcinoma specimen resulted in the discovery of *EML4-ALK* as a fusion-type oncogene (Figs. 1 and 2; ref. 17).

EML4 and *ALK* loci both map to the short arm of human chromosome 2 in opposite orientations and are separated by a distance of approximately 12 Mbp. A small inversion, inv(2)(p21p23), affecting both loci gives rise to the fusion gene. *EML4-ALK* was the first recurrent fusion-type oncogene in NSCLC, and, together with *ETS* fusions in prostate cancer (25), its existence argues against the previous notion that oncogenesis mediated by chromosome rearrangement is relatively specific to hematologic malignancies and sarcomas (rather than epithelial tumors).

EML4-ALK encodes a protein consisting of an amino-terminal portion of EML4 fused to the intracellular portion of ALK. *EML4-ALK* undergoes constitutive dimerization mediated through the coiled-coil domain of the EML4 portion and thereby acquires transforming ability in a manner

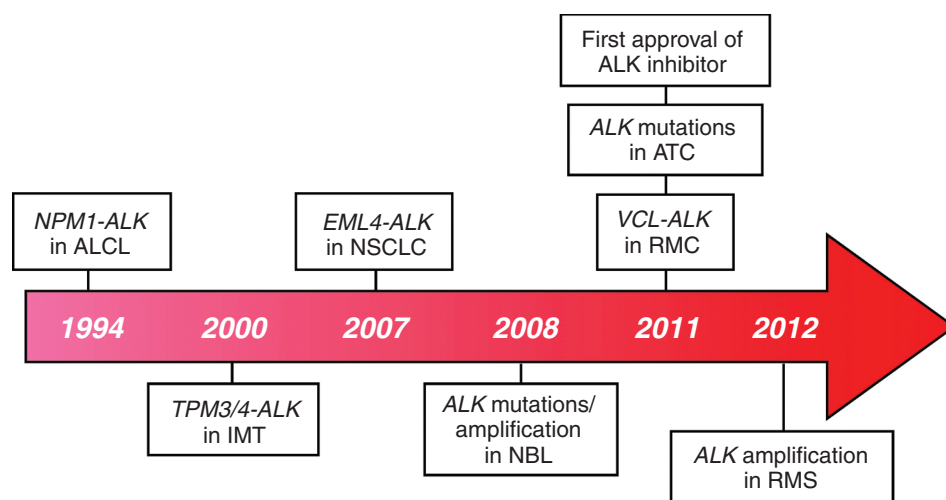


Figure 2. History of ALK in oncology. The first discovery of an oncogenic mutant of ALK was that of *NPM1-ALK* associated with ALCLs in 1994, which was followed by the identification of *TPM3/4-ALK* associated with IMTs, *EML4-ALK* associated with NSCLCs, mutated/amplified ALK associated with neuroblastoma (NBL), *VCL-ALK* associated with RMCs, mutated ALK associated with ATCs, and amplified ALK associated with rhabdomyosarcoma (RMS). Whereas several ALK inhibitors are currently in clinical trials, one such compound, crizotinib, was approved as a therapeutic drug for ALK-rearranged NSCLCs in 2011.

dependent on the associated upregulation of PTK activity. Indeed, several cell lines positive for *EML4-ALK* were found to be dependent on ALK catalytic activity for their proliferation (26, 27). Furthermore, transgenic mice that express *EML4-ALK* in lung type II alveolar cells manifest hundreds of adenocarcinoma nodules in both lungs soon after birth, and treatment of the animals with an ALK inhibitor results in the rapid clearance of these nodules (28). Such successful treatment of *EML4-ALK* transgenic mice with an ALK inhibitor was subsequently confirmed independently (29). These data suggested that *EML4-ALK* is the essential growth driver for NSCLC positive for this fusion kinase, and that targeting of ALK activity may therefore prove therapeutically effective in the clinic.

Clinicopathologic Features and Diagnosis of *EML4-ALK*-Positive Tumors

EML4-ALK is present in 3% to 6% of NSCLC cases (30–32). Of note, the clinical characteristics of patients with NSCLCs positive for *EML4-ALK* are similar to those of such individuals who harbor activating mutations in the EGF receptor gene (*EGFR*): Both groups of patients thus tend to manifest an adenocarcinoma histology and to be non- or light smokers. However, the presence of *EML4-ALK* and that of *EGFR* or *KRAS* mutations are mutually exclusive, albeit with rare exceptions (33). Furthermore, whereas NSCLC with *EGFR* mutations is more prevalent in Asian populations than in Caucasians, no such ethnic differences have been reported for NSCLCs with *EML4-ALK*. With regard to pathologic characteristics, *EML4-ALK*-positive NSCLC has been found to contain signet-ring cells or to manifest a mucinous cribriform pattern (34–36), but other pathologic subtypes of NSCLCs also may harbor *EML4-ALK*. *EML4-ALK* may be infrequently present in other types of human cancers (16, 37).

The original *EML4-ALK* we identified resulted from ligation of intron 13 of *EML4* to intron 19 of *ALK* (17), but many other variants of the fusion gene have since been described. The vast majority of *ALK* translocations, including *EML4-ALK*, *NPM1-ALK*, and *TPM3-ALK*, involve intron 19 of *ALK*. Theoretically, ligation of *EML4* introns 1, 2, 6, 13, 18, 20, or 21 to intron 19 of *ALK* should generate an in-frame fusion at the mRNA level. Furthermore, given that exon 2 of *EML4* encodes the coiled-coil domain essential for *EML4-ALK* activation, all such fusions with the exception of that of *EML4*

intron 1 would be expected to generate an oncogenic kinase. Large-scale screening of clinical specimens has revealed that the original *EML4-ALK* variant (referred to as E13;A20 or variant 1) together with a variant in which intron 6 of *EML4* is fused to intron 19 of *ALK* (referred to as E6;A20 or variant 3; ref. 26) account for more than 90% of all *EML4-ALK*-positive cases of NSCLCs in Japan (M. Soda, personal communication), but many rare variants have also been identified (17, 26, 27, 30, 31, 34, 37, 38).

Importantly, *EML4* exons theoretically unable to undergo in-frame fusion to exon 20 of *ALK* may be involved in the generation of oncogenic *EML4-ALK* proteins. For instance, an *EML4-ALK* cDNA in which exon 14 of *EML4* is fused in-frame to the 13th nucleotide of *ALK* exon 20 has been identified (30). In addition, another variant in which the nucleotide located 19 bp upstream of the 3' end of *EML4* exon 15 is fused to that located 20 bp downstream of the 5' end of *ALK* exon 20 was described (27). It is therefore important that clinics adopt diagnostic techniques, such as those based on multiplex reverse transcription PCR (RT-PCR), that are able to capture all these variants of *EML4-ALK* reliably.

Currently, no single technique may be suitable for the analysis of all specimen types. Immunohistochemistry and FISH, for example, are applicable to formalin-fixed, paraffin-embedded (FFPE) tissue specimens (32, 34, 35) but may not be suitable for the analysis of sputum, pleural effusion, bronchial lavage fluid, or frozen tissue. Conversely, the latter specimen types are readily examined by RT-PCR (30), whereas the former ones may not be suitable for this technique. I thus propose that diagnostic tools for the detection of *EML4-ALK* should be selected on the basis of the available specimen types. FISH and immunohistochemistry should be applied to FFPE tissue samples, whereas multiplex RT-PCR is appropriate for the other specimen types.

Crizotinib

The first ALK inhibitor to enter clinical trials was crizotinib, which is also known as PF-02341066 and is actually a dual inhibitor for both ALK and MET kinases (Table 1; ref. 39). At the time of the discovery of *EML4-ALK*, crizotinib had already entered a phase I trial that mainly targeted digestive tract cancers positive for *MET* amplification. After the report of *EML4-ALK*, the phase I trial with crizotinib was expanded to include tumors positive for ALK rearrangement, and the drug soon proved as therapeutically efficacious for such tumors.

Table 1. ALK inhibitors under clinical trials or already approved

Inhibitor	Company	Trial phase	References
Crizotinib	Pfizer	Phase III (approved in United States, South Korea, and Japan)	39, 68
CH5424802	Chugai Pharmaceutical	Phase I/II	62
ASP3026	Astellas Pharma	Phase I	Not available
LDK378	Novartis	Phase I	Not available
AP26113	Ariad	Phase I/II	61

The response rate for crizotinib in patients with *ALK*-rearranged NSCLCs in the trial was shown to be 57%, with a disease control rate of up to 90% (32). Furthermore, the median overall survival for crizotinib treatment was not determinable within the follow-up period of 18 months (40). Comparison of crizotinib treatment with a historical control was further striking. Whereas the median overall survival was not achieved for patients who received crizotinib as a second- or third-line treatment, it was only 6 months for the *ALK*-rearranged control patients who received conventional chemotherapy in the second- or third-line setting.

While crizotinib can inhibit MET kinase activity and *MET* may become amplified in NSCLCs (41), there was no *MET* amplification present in the above *EML4-ALK*-positive cohort (32). Similarly, while ROS1 tyrosine kinase is sensitive to crizotinib (42), a recent large-scale screening of gene fusions among NSCLC ($n = 1,529$) revealed a complete mutual exclusiveness between *ALK* and *ROS1* fusions (43). Furthermore, the mechanism for the insensitivity of *ALK* fusion-positive tumors to crizotinib has been mostly secondary mutations within the kinase domain of *EML4-ALK* (see below). These data evidence that crizotinib exerts its marked therapeutic efficacy in NSCLCs through specific suppression of *EML4-ALK* activity.

These observations clearly supported the clinical use of *ALK* inhibitors for the treatment of *EML4-ALK*-positive NSCLC. Indeed, on August 26, 2011, the U.S. Food and Drug Administration approved crizotinib as a treatment for *ALK*-rearranged NSCLCs. From the time of our first report of the identification of *EML4-ALK* in 2007, it took only 4 years for the first *ALK* inhibitor to be approved for use in the clinic, which is a record for cancer drug development (44).

OTHER *ALK* TRANSLOCATIONS IN EPITHELIAL TUMORS

Following the discovery of *EML4-ALK*, efforts have expanded to detect novel *ALK* fusions in epithelial tumors. Development of a sensitive immunohistochemical technique (intercalated antibody-enhanced polymer method, or iAEP) to stain *ALK* proteins in FFPE specimens led to the identification of several NSCLC samples that were positive with this approach but negative for *EML4-ALK* with multiplex RT-PCR (34). Further investigation of these specimens revealed the presence of another fusion of *ALK*, *KIF5B-ALK*. Similar to *EML4-ALK*, *KIF5B* contains dimerization motifs that play an essential role in the oncogenic activity of *KIF5B-ALK* and there are now known to be several variants of *KIF5B-ALK* (45). Togashi and colleagues reported still another *ALK* fusion, *KLC1-ALK*, in NSCLCs (46).

Yet another novel *ALK* fusion, *VCL-ALK*, was recently identified in a tumor of unclassified renal cell carcinoma with renal medullary carcinoma (RMC) characteristics that developed in a 16-year-old boy with sickle cell trait (47). *VCL-ALK* was also detected in RMCs isolated from a 6-year-old boy (48). RMC mostly affects young individuals and has a poor outcome, but the discovery of *VCL-ALK* has raised the possibility of effective treatment with an *ALK* inhibitor for patients who harbor this fusion gene. Furthermore, screening of tissue microarrays of renal cell carcinoma with the iAEP technique led to the detec-

tion of single cases each positive for *TPM3-ALK* or *EML4-ALK* (E2;A20 variant; ref. 16).

ONCOGENIC POINT MUTATIONS IN *ALK*

Neuroblastoma

Attempts by several groups to identify genes underlying neuroblastoma through different approaches (mapping of single-nucleotide polymorphisms for familial neuroblastoma and chromosome copy number analysis for sporadic neuroblastoma) resulted in the almost simultaneous identification of activating mutations within *ALK* (Figs. 2 and 3; refs. 18–21). About 10% of sporadic neuroblastoma cases harbor somatic nonsynonymous mutations within *ALK*, including K1062M, F1174L/C/I, F1245C/V/L, and R1275Q amino acid substitutions. On the other hand, a distinct but partially overlapping set of *ALK* mutations (T1087I, G1128A, R1275Q, and others) has been identified in familial neuroblastoma.

Importantly, these mutations do not confer equal transforming ability. The F1174L mutant, for instance, efficiently phosphorylates the signaling molecules STAT3 and AKT, but not extracellular signal-regulated kinase (ERK)1/2, whereas the R1275Q mutant efficiently phosphorylates ERK1/2 but not STAT3 (18). Knockdown experiments revealed that the growth of neuroblastoma cell lines was dependent to a greater extent on the F1174L mutant than on R1275Q (18, 20). The mutant *ALK* proteins thus contribute substantially to the transformation process in neuroblastoma, but the extent to which they do so varies among the mutation types.

These mutations also differentially affect the sensitivity of neuroblastoma to *ALK* inhibitors (49, 50), which may not be surprising given that point mutations within the kinase domain of *ALK* affect its 3-dimensional structure (including that of the inhibitor binding cleft) and thereby influence inhibitor binding. The F1174L mutant confers marked resistance to crizotinib in a cell-based assay (49, 50), suggesting that this amino acid substitution not only increases the enzymatic activity of *ALK* by changing the structure of the kinase domain but by doing so also affects the binding of *ALK* inhibitors.

The I1250T mutation of *ALK* was recently identified in an individual with neuroblastoma and was shown to abolish the activity of the enzyme (51). Each *ALK* mutation identified in neuroblastoma therefore needs to be assessed for how (or if) it contributes to carcinogenesis.

Anaplastic Thyroid Cancer

Nucleotide sequencing of *ALK* exons encoding the kinase domain in cell lines and fresh specimens of thyroid cancer (52) revealed novel missense mutations specifically in anaplastic thyroid cancer (ATC) samples (2 positive samples of 11). Each of the 2 identified amino acid substitutions (L1198F and G1201E) increased the enzymatic activity of *ALK* and induced the formation of transformed foci when introduced into mouse 3T3 cells, clearly indicating the activating nature of these mutations. It is thus likely that a subset of ATC and neuroblastoma cases share the same transforming gene, but it remains to be determined whether the *ALK* mutation profiles differ between the 2 disorders.

GENE AMPLIFICATION OF ALK

In addition to nonsynonymous mutations, *ALK* infrequently becomes amplified in neuroblastoma (21, 53). While its clinical relevance is yet to be clarified, *ALK* amplification frequently co-occurs with amplification of *MYCN* amplification, a known growth driver for this disorder, suggesting that *ALK* also contributes to carcinogenesis.

Recently, van Gaal and colleagues (54) have discovered frequent copy number gain of *ALK* in rhabdomyosarcoma accompanied with an increased level of ALK protein. In some cases, *ALK* copy number was even above 10. Interestingly, contrary to neuroblastoma, rhabdomyosarcoma with *ALK* amplification do not carry *MYCN* amplification. Such *ALK* anomaly is likely to be connected to carcinogenesis because *ALK* gain was associated with poor survival and the occurrence of metastases. In addition, van Gaal and colleagues also identified one case with *ALK* (D1225N) and 7 with *ALK* frameshift mutations of 43 rhabdomyosarcoma specimens, although clinical relevance of such mutations is yet to be examined.

RESISTANCE TO ALK INHIBITORS

Some *EML4-ALK*-positive NSCLC tumors are insensitive to initial treatment with ALK inhibitors, whereas others acquire resistance to these drugs after initial successful treatment. Information on the molecular mechanisms underlying such resistance remains limited.

The first insight into such resistance mechanisms was provided by analysis of an individual with *EML4-ALK*-positive NSCLC who initially showed a partial response to crizotinib treatment but underwent a rapid relapse after 5 months. *EML4-ALK* cDNA was amplified by PCR from tumor specimens obtained before the onset of treatment and after relapse, and it was then subjected to deep sequencing with a next-generation sequencer. Comparison of the 2 data sets resulted in the identification of 2 nonsynonymous mutations present only in the latter specimen. Interestingly, these 2 amino acid substitutions (C1156Y and L1196M) were found to independently confer resistance to crizotinib and other ALK inhibitors (55).

Neither C1156Y nor L1196M affects the enzymatic activity of *EML4-ALK*. NSCLC cells harboring either mutant might therefore be positively selected *in vivo* only in the presence of ALK inhibitors. Furthermore, Leu¹¹⁹⁶ is the “gatekeeper” site buried deeply within the ATP-binding pocket of ALK, with the corresponding sites of EGFR (Thr⁷⁹⁰) and BCR-ABL1 (Thr³¹⁵) being the most frequently mutated residues associated with gefitinib and imatinib resistance, respectively (56).

Examination of a similar *EML4-ALK*-positive individual who initially responded to crizotinib but later acquired resistance revealed the presence in post-relapse *EML4-ALK* cDNA of a mutation resulting in an L1152R substitution in the kinase domain (57). Another mutation conferring drug resistance (F1174L) was identified in a case of RANBP2-*ALK*-positive IMTs (58). Of note, F1174L is also one of the frequent amino acid substitutions identified in neuroblastoma (Fig. 3). Further extensive screening of crizotinib-resistant mutations among 18 relapsed patients revealed 4 secondary mutations (I151Tins, L1196M, G1202R, and S1206Y) within the kinase domain of *EML4-ALK*, all of which confer resistance to ALK

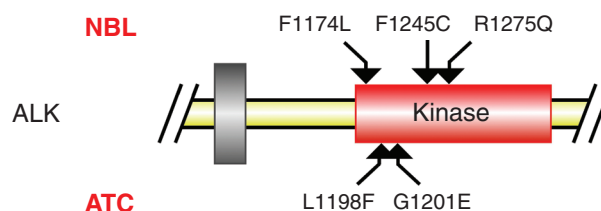


Figure 3. Missense mutations in ALKs. Activating mutations of ALKs are associated with familial and sporadic neuroblastoma (NBL). A different set of missense mutations is also associated with a subset of ATC tumors. Representative mutations for each disorder are shown according to their location in the kinase domain of ALK.

inhibitors (59). Such investigation further identified a high-level amplification of *EML4-ALK* in one patient, suggesting another mechanism (gene amplification) of drug insensitivity.

Another screening of *EML4-ALK*-positive tumors at a relapsed phase led to the identification of L1196M (in 2 of 14 resistant cases) and G1269A (in 2 cases) mutations accounting for the acquired drug resistance, and of gene amplification in 2 cases (60). Interestingly, in this cohort, some tumors lost *EML4-ALK* oncogene at the relapsed phase, but instead acquired activating *EGFR* or *KRAS* mutations. Whether such oncogenes other than *EML4-ALK* were present in a minor population of the original tumor or secondarily acquired during the crizotinib treatment remains elusive.

As of March 2012, 5 distinct ALK inhibitors are in clinical trials worldwide (Table 1), with some of these drugs showing inhibitory activity *in vitro* even with the gatekeeper mutant (61, 62). It will thus be of interest to determine whether treatment with such inhibitors results in the development of acquired resistance or not.

ALKOMA: A STEP TOWARD GENETIC INFORMATION-BASED CANCER CLASSIFICATION

Since the initial discovery of NPM1-*ALK* in 1994, our knowledge of the role of ALK in human cancer has increased markedly. We now recognize the contribution of ALK to an unexpectedly wide range of tumors, with *ALK* translocations underlying lymphoma, lung carcinoma, kidney cancer, and soft tissue tumors and *ALK* mutations being responsible for neuronal and thyroid cancer and *ALK* amplification frequently occurring in rhabdomyosarcoma.

Given that all ALK fusion kinases retain an intact ATP-binding pocket (where most ALK inhibitors bind), it is likely that ALK inhibitors will be effective against any tumor type that harbors such an ALK fusion (63, 64). From the standpoint of pharmaceutical companies, the fact that a single compound can serve as a magic pill for many different types of cancer in different organs is sufficiently compelling to warrant the development of such drugs even if the individual cancer types do not have a high incidence.

For neuroblastoma and ATC, however, the efficacy of an ALK inhibitor may be substantially influenced by the type or position of the missense mutation. However, given that ALK is a transmembrane protein, the mutant proteins may

be effectively targeted by antibodies (65), as is the case for other transmembrane proteins targeted by the antibodies rituximab and trastuzumab.

Genetic information was first integrated into the classification of hematologic malignancies. For instance, whereas acute myeloid leukemia (AML) had previously been divided into subgroups with distinct differentiation profiles (assessed by pathologic analyses), AML harboring *RUNX1-RUNX1T1*, *PML-RARA*, or *MLL* rearrangements is now defined as a distinct entity according to the current World Health Organization classification (66). Likewise, all-*trans* retinoic acid is highly effective only in the treatment of retinoic acid receptor alpha (encoded by *RARA*) fusion-positive AML, acute promyelocytic leukemia (APL). Similarly, ABL1 inhibitors are only used against *BCR-ABL1*-positive CML/acute lymphoblastic leukemia. It is likely that tumor cells of APL or CML are deeply addicted to the activity of PML-RARA or BCR-ABL1, respectively. Therefore, single reagents targeting individual oncoproteins have a profound therapeutic effect.

In the treatment of epithelial tumors, single EGFR inhibitors provide a high response rate to NSCLCs harboring activating *EGFR* mutations as well. Importantly, treatment with such EGFR inhibitors worsens the prognosis of NSCLC without *EGFR* mutations (67). Targeted drugs are, thus, likely to be highly effective only against tumors in which corresponding targets carry activating mutations and become “essential growth drivers” for the cancer. The definition of essential growth drivers for given oncogenes is difficult because treatment efficacy for cell lines *in vitro* does not always recapitulate that in clinics. For instance, while inhibitors against RAS or PIK3CA are able to suppress the growth of cancer cell lines, these compounds have failed to provide such efficacy in humans.

Therefore, significant response in patients by a monotherapy with a targeted drug should be a faithful indicator for the corresponding target to be the essential growth driver. Unfortunately, however, such clinically proven drivers are still few, but EML4-ALK is a newcomer to this growing list. Importantly, other ALK fusions, NPM1-ALK and RANBP2-ALK, are likely the essential growth drivers as well, because the crizotinib monotherapy has a profound therapeutic effect (63, 64). I propose that these tumors be collectively referred to as “ALKoma,” in which abnormal ALK plays an indispensable component in the carcinogenesis.

Interestingly, the term “ALKoma” encompasses multiple organs. NSCLCs, IMTs, and ALCLs were once regarded as completely distinct clinical entities affecting different organs. However, it is now known that a fraction of each of these cancer types shares activated ALK as the essential growth driver and such tumors can be targeted for treatment with ALK inhibitors (32, 63, 64). Because of the similar protein structure to that of EML4-ALK/NPM1-ALK/RANBP2-ALK, VCL-ALK in RMCs should be a good candidate for the next member of ALKoma. Data from ongoing clinical trials with crizotinib for neuroblastoma will also tell us whether activated ALK with nonsynonymous mutations is also a strong driver for this disorder. The term “ALKoma” has the advantage that it indicates the preferred treatment for the tumor. It is thus a good example of genetic information-based “beyond organ” cancer classification, many other examples of which may emerge in the future.

Disclosure of Potential Conflicts of Interest

H. Mano has commercial research grant from Astellas Pharma and Illumina Inc.; Ownership Interest (including patents); and serves as a scientific advisor for Pfizer Inc., Astellas Pharma, Chugai Pharmaceutical, and Daiichi Sankyo Co., Ltd., and is an CEO of CureGene Co., Ltd.

Author's Contributions

Conception and design: H. Mano

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H. Mano

Writing, review, and/or revision of the manuscript: H. Mano

Study supervision: H. Mano

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